Remarks

Claims 1-15 and 50-53 are pending in this application. Applicants submit that all of the claims are allowable for the reasons discussed below.

Applicants first wish to thank the Examiner for the courtesy she extended Max Bachrach and Hoon Choi, attorneys for Applicants, during a telephone conversation held on July 17, 2003. As discussed during the conversation, Applicants respectfully disagree with the Examiner's belief that the pending claims read on the administration of ziprasidone. Applicants respectfully submit the following remarks further to that conversation and further to the final Office Action mailed June 18, 2003.

The Rejection Under 35 U.S.C. § 102 Should Be Withdrawn

The rejection of claims 1-4 and 6-9 under 35 U.S.C. § 102 over Davis *et al.*, *CNS Drugs*, 8(2): 513-159 (1997) ("Davis") is maintained in this final Office Action. It is alleged that because Davis discloses ziprasidone as an antipsychotic drug, and the administration of ziprasidone metabolites is allegedly inherent to the administration of ziprasidone itself, claims 1-4 and 6-9 are anticipated. Applicants respectfully traverse this rejection.

As Applicants stated in their previous response, the administration of ziprasidone metabolites is not inherently anticipated by the administration of ziprasidone itself. This is because the term "administration," as understood by one of ordinary skill in the art, requires the existence of a compound prior to its administration. The Patent Office has long recognized this fact.[1] The Court of Appeals for the Federal Circuit has also recognized this fact. *See Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 2003 WL 21767852 (Fed. Cir.), a copy of which is enclosed herewith.

Schering concerned the patentability of claims directed to descarboethoxyloratadine ("DCL"), a metabolite of the known drug loratadine. *Id.* at *1. The record showed that DCL "necessarily and inevitably forms from loratadine under normal conditions." *Id.* at *4. Therefore, DCL is "a necessary consequence of administering loratadine to patients." *Id.* The court held that a claim directed to DCL itself was anticipated by a prior art patent that discloses loratadine. However, the court

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[1] *See, e.g.*, U.S. Patent No. 6,342,496, which claims a method of treating a cerebral function disorder by administering a bupropion metabolite. *See also* U.S. Patent No. 6,468,997, which claims a method of treating various disorders by administering N-desmethylolanzapine, a metabolite of olanzapine.

devoted an entire section of its opinion to a discussion of metabolite claims that may be patentable:

> [T]his court's conclusion on inherent anticipation in this case does not preclude patent protection for metabolites of known drugs.
>
> * * *
>
> A skilled patent drafter ... might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form, ... or as a pharmaceutical composition (e.g., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition. The [prior art] patent would not provide an enabling disclosure to anticipate such claims because, for instance, the [prior art] patent does not disclose isolation of DCL.

Id. at *7 (emphasis added). In other words, a method of administering a metabolite of a known compound may be patentable even where the metabolite "necessarily and inevitably" forms from the administration of the parent compound.

The claims pending in this application are of the sort expressly permitted by the Federal Circuit. These claims are directed to methods of treating various disorders comprising the administration of a ziprasidone metabolite. As the Federal Circuit recognized, such claims do not encompass the administration of the parent drug ziprasidone. Therefore, because Davis does not disclose the administration of a ziprasidone metabolite, Applicants respectfully request that the rejection under 35 U.S.C. § 102 be withdrawn.

The Rejection Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 1-15 and 50-53 are rejected under 35 U.S.C. § 103 as allegedly obvious over Davis in view of U.S. Patent No. 4,831,031 to Lowe *et al.* ("Lowe"), U.S. Patent No. 5,312,925 to Allen *et al.* ("Allen"), and Prakash *et al.*, *Drug Metabolism and Disposition*, 25(7): 863-871 (1997) ("Prakash"). Applicants respectfully traverse this rejection for the following reasons.

The Patent Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. *In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir. 1995); *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993). To establish a *prima facie* case of obviousness, the Patent Office must first show that the prior art suggested to those of

ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, it must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant' s disclosure. Third, the Patent Office must show that the prior art teaches or suggests all the claim limitations. MPEP § 2143; *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). These criteria must be satisfied with factual and objective evidence found in the prior art: an examiner's conclusory statements cannot form a basis for a *prima facie* case of obviousness. *In re Sang-Su Lee*, 277 F.3d 1338, 1343-4 (Fed. Cir. 2002).

Applicants, in their response to the previous Office Action of November 5, 2002, stated that there would have been no motivation to combine Davis, Lowe and Allen because ziprasidone metabolites were known to be inactive. The Examiner, citing Prakash, responds that ziprasidone sulfoxide and ziprasidone sulfone were known to exhibit affinities for 5-HT_2 and D_2 receptors.

Presumably, the Examiner is relying on the statement in Prakash that "[t]he affinities of the sulfoxide and sulfone metabolites for 5-HT_2 and D_2 receptors are low with respect to ziprasidone ..." Prakash, page 2, lines 5-6 (emphasis added).[2] However, Prakash goes on to state that these metabolites are "thus unlikely to contribute to [ziprasidone's] antipsychotic effects." *Id.* (emphasis added). This statement is consistent with the disclosure of Ereshefesky, *J. Clin. Psychiatry*, 57 (suppl. 11): 12-25 (1996),[3] as well as *Physician's Desk Reference*, 56th Ed., page 2688 (2002), a copy of which is enclosed herewith. Both references teach that the activity of ziprasidone is due to ziprasidone itself, rather than its metabolites. As the Examiner is well aware, "a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention." MPEP § 2141.02, citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (*emphasis in the original*). Therefore, Prakash, like other prior art references, taught away from the claimed invention. Because one of ordinary skill in the art would

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[2] The citation is made to the copy of Prakash submitted by Applicants in their Information Disclosure Statement of April 9, 2001.

[3] A copy was provided with Applicants' response to the previous Office Action of November 5, 2002.

have had no motivation to combine the cited references, much less any expectation of successfully obtaining the claimed invention, Applicants respectfully request that the rejection under 35 U.S.C.
§ 103 be withdrawn.

This rejection should be withdrawn for additional reasons. It is contended in the Office Action that since ziprasidone and ziprasidone salts (*i.e.*, ziprasidone hydrochloride) are known neuroleptic agents, it would have been obvious to employ ziprasidone or any of its known salts or metabolites in treating neuroleptic disorders. A salt form of a compound, however, is completely different from a metabolite of the compound.[4] Therefore, Applicants respectfully point out that this rejection, insofar as it is based on the Examiner's unsupported conclusory statement, cannot be maintained. *In re Sang-Su Lee*, 277 F.3d at 1343-4.

Finally, Applicants again submit that the Examiner's reliance on *Zenith Labaratories Inc. v. Bristol-Myers Squibb Co.*, 30 USPQ2d 1285 (Fed. Cir. 1994) in rejecting the claims under § 103 is misplaced. In responding to the fact that *Zenith* concerned patent infringement, not patent validity, the Examiner argues that the court's reasoning is applicable here because the question before the court was the relationship between pre-ingested and ingested from of a drug. However, Applicants point out that that relationship was only addressed in the context of patent infringement, *i.e.*, whether the *in vivo* formation of a specific hydrate would infringe a claim directed to that hydrate. The case did not concern the patentability of a hydrate, much less a metabolite. Indeed, the *Zenith* court expressly stated that "[t]he question before us is not one of validity: whether the claim would be patentable over the prior art ... The question here is one of infringement." *Zenith*, 30 USPQ2d at 1289 (emphasis added). Moreover, since *Zenith*, the Federal Circuit has made it clear that the prior art disclosure of a compound does not preclude the patentability of claims directed to the administration of its metabolites. *See Schering* at *7. Thus, Applicants respectfully submit that the rejection under 35 U.S.C.

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[4] Whereas it is well known that a salt form of a compound does not affect the pharmacological activity of a compound, a metabolite of that compound, which usually involves substantial chemical modification (*e.g.*, deletion, addition or replacement of covalently attached chemical groups) does not necessarily have pharmacological properties identical to the parent compound. Thus, a blanket assertion that use of a salt or a metabolite of ziprasidone would have been obvious, merely because a ziprasidone salt was known to be active, cannot be made. Should the Examiner disagree, Applicants respectfully request that she set forth her factual assertions in an affidavit under 37 C.F.R. 1.104(d)(2). *See* MPEP § 2144.03.

§ 103 should be withdrawn.

Conclusion

Applicants respectfully submit that all claims currently pending in this application are allowable, and request that their rejections be withdrawn.

No fee is believed due for this submission. Should any additional fees be required for this submission or to avoid abandonment of the application, please charge such fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date August 18, 2003

45,479
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2003 WL 21767852
--- F.3d ---
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Only the Westlaw citation is currently available.

United States Court of Appeals,
Federal Circuit.

SCHERING CORPORATION, Plaintiff-Appellant,
v.
GENEVA PHARMACEUTICALS, INC. and Novartis Corporation, and Teva Pharmaceuticals USA, Inc., and Andrx Corporation, Andrx Pharmaceuticals LLC, and Andrx Pharmaceuticals, Inc., and Mylan Pharmaceuticals, Inc., and Wyeth, ESI-Lederle, Wyeth Pharmaceuticals, and Wyeth Consumer Healthcare (formerly American Home Products Corporation, Wyeth-Ayerst Laboratories, and Whitehall Robbins Healthcare), and Impax Laboratories, Inc., Apotex, Inc. and Novex Pharma, Copley Pharmaceutical, Inc., and Genpharm, Inc., Defendants-Appellees.

Nos. 02-1540, 02-1541, 02-1542, 02-1543, 02-1544, 02-1545, 02-1546, 02-1547, 02-1548, 02-1549, 03-1021, 03-1022, 03-1023, 03-1025, 03-1027.

Aug. 1, 2003.

Owner of patent for antihistamine metabolite sued manufacturers of generic versions for infringement. The United States District Court for the District of New Jersey, 2002 WL 2001552, John W. Bissell, Chief Judge, held that patent was invalid, and appeal was taken. The Court of Appeals, Rader, Circuit Judge, held that patent was inherently anticipated by prior art patent for underlying antihistamine.

Affirmed.

[1] Federal Courts ⇦0

170Bk0 k.

Grant of summary judgment is reviewed without deference.

[2] Patents ⇦0
291k0 k.

Patent is invalid for anticipation if single prior art reference discloses each and every limitation of claimed invention.

[3] Patents ⇦0
291k0 k.

Prior art reference may anticipate patent without disclosing feature of claimed invention if that missing characteristic is necessarily present, or inherent, in single anticipating reference.

[4] Patents ⇦0
291k0 k.

Inherent anticipation of later patent does not require that person of ordinary skill in art at time would have recognized inherent disclosure.

[5] Patents ⇦0
291k0 k.

Patent for metabolite of previously patented antihistamine was inherently anticipated, even though prior patent did not disclose any compound identifiable as claimed invention; metabolite necessarily and inevitably formed upon ingestion of previously patented antihistamine under normal conditions.

[6] Patents ⇦0
291k0 k.

Inherency operates to anticipate entire inventions as well as single limitations within patented inventions.

[7] Patents ⇦0
291k0 k.

Patent anticipation does not require actual creation or reduction to practice of prior art subject matter; anticipation requires only enabling disclosure.

[8] Patents ⇦0
291k0 k.

Prior patent for antihistamine contained enabling disclosure of metabolite formed when drug was ingested, and thus anticipated later patent for that

metabolite; although prior patent did not mention metabolite, it did disclose administration of antihistamine to patient.

[9] Patents ⚿0
291k0 k.

Broad compound claims are inherently anticipated by prior art disclosure of pharmaceutical drug that metabolizes into claimed compound.

Patents ⚿328(2)
291k328(2) Most Cited Cases

4,282,233. Cited as Prior Art.

Patents ⚿328(2)
291k328(2) Most Cited Cases

4,659,716. Invalid.
Appealed from United States District Court for the District of New Jersey, John W. Bissell, Chief Judge.

Robert G. Krupka, Kirkland & Ellis, of Los Angeles CA, argued for plaintiff-appellant. Of counsel on the brief were David P. Swenson, Kirkland & Ellis, of Washington, DC; John M. Desmarais, Sandra A. Bresnick, Peter J. Armenio, Maxine Y. Graham, Monica V. Bhattacharyya, and Young J. Park, Kirkland & Ellis, of New York, NY. Of counsel were John F. Hoffman and Arthur Mann, Schering Corporation, of Kenilworth, NJ.

Robert D. Bajefsky, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., of Washington, DC, argued for defendants-appellees Wyeth, ESI-Lederle, Wyeth Pharmaceuticals and Wyeth Consumer Healthcare (formerly American Home Products Corporation, Wyeth-Ayerst Laboratories, and Whitehall Robbins Healthcare). With him on the brief were Barbara R. Rudolph and Matthew J. Mason. Of counsel on the brief were David A. Manspeizer and Lawrence Alaburda, Wyeth, of Madison, NJ. On the brief was Julie A. Petruzzelli, Venable, Baetjer, Howard, & Civiletti, LLP, of Washington, DC, for defendant- appellee Impax Laboratories, Inc. Of counsel were Peter J. Curtin and James E. Gray. Also on the brief were Edgar H. Haug, Daniel G. Brown, and Porter F. Fleming, Frommer Lawrence & Haug LLP, of New York, NY; for defendant-appellee Genpharm Inc.; Colin A. Underwood, Soloman, Zauderer, Ellenhorn, Frischer & Sharp, of New York, NY, for defendants-appellees Andrx Corporation, Andrx Pharmaceuticals LLC, and Andrx Pharmaceuticals, Inc.; E. Anthony Figg, Joseph A. Hynds, Rothwell, Figg, Ernst & Manbeck, of Washington, DC, for defendant-appellee Mylan Pharmaceuticals, Inc.

Robert S. Silver and William J. Castillo, Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd., of Philadelphia, PA, for defendants-appellees Apotex, Inc. and Novex Pharma.

Thomas L. Creel, Goodwin Procter, LLP, of New York, NY, for defendants- appellees Teva Pharmaceuticals USA, Inc. and Copely Pharmaceutical, Inc. With him on the brief were Frederick H. Rein and Keith A. Zullow.

Douglass C. Hochstetler, Schiff, Hardin & Waite, of Chicago, IL, argued for defendants-appellees Geneva Pharmaceuticals, Inc. and Novartis Corporation. With him on the brief were Patricia J. Thompson and Jo-Anne M. Kokoski. Of counsel on the brief was Kevin M. Flowers, Ph.D., Marshall Gerstein & Borun, of Chicago, IL.

Before RADER, Circuit Judge, PLAGER, Senior Circuit Judge, and BRYSON, Circuit Judge.

RADER, Circuit Judge.

*1 On summary judgment, the United States District Court for the District of New Jersey determined that claims 1 and 3 of U.S. Patent No. 4,659,716 (the '716 patent) are invalid. *Schering Corp. v. Geneva Pharm., Inc.*, No. 98-1259 (D.N.J. Aug.8, 2002). Because the district court correctly found that U.S. Patent No. 4,282,233 (the '233 patent) inherently anticipates claims 1 and 3 of the ' 716 patent, this court affirms.

I.

Schering Corporation (Schering) owns the '233 and '716 patents on antihistamines. Antihistamines inhibit the histamines that cause allergic symptoms.

The prior art '233 patent covers the antihistamine

loratadine, the active component of a pharmaceutical that Schering markets as CLARITINTM. Unlike conventional antihistamines when CLARITINTM was launched, loratadine does not cause drowsiness.

The more recent '716 patent at issue in this case covers a metabolite of loratadine called descarboethoxyloratadine (DCL). A metabolite is the compound formed in the patient's body upon ingestion of a pharmaceutical. The ingested pharmaceutical undergoes a chemical conversion in the digestion process to form a new metabolite compound. The metabolite DCL is also a non-drowsy antihistamine. The '716 patent issued in April 1987 and will expire in April 2004 (the '233 patent issued in 1981 and has since expired). *See* 35 U.S.C. § 154(c)(1) (2000) (defining the term of a patent in force before June 8, 1995, as the greater of twenty years from the earliest U.S. priority date or seventeen years from grant).

Structurally, loratadine and its metabolite DCL differ only in that loratadine has a carboethoxy group (i.e., -COOEt) on a ring nitrogen, while DCL has a hydrogen atom on that ring nitrogen:

Claim 1 of the '716 patent covers DCL (for X = Cl), its fluorine analog, and their salts; claim 3 covers only DCL and its salts:

1. A compound of the formula
or a pharmaceutically acceptable salt thereof, wherein X represents Cl or F.
3. A compound having the structural formula
or a pharmaceutically acceptable salt thereof.

The '233 patent issued on August 4, 1981, over one year before the earliest priority date of the '716 patent, February 15, 1984. The '233 patent is thus prior art to the '716 patent. *See* 35 U.S.C. § 102(b) (2000) ("A person shall be entitled to a patent unless ... the invention was patented ... in this or a foreign country ... more than one year prior to the date of the application for patent in the United States."). The '233 patent discloses a class of compounds including loratadine (disclosed in Example 1B). '233 patent, col. 3, ll. 5-12. The '233 patent claims loratadine in claim 7. *Id.*, col. 6, ll. 38-40. The '233 patent claims four other compounds in claims 8-11. Examples 6-7 are prophetic [FN1] examples of pharmaceutical compositions (a syrup and a tablet), each containing an unidentified "active compound." The '233 patent does not expressly disclose DCL and does not refer to metabolites of loratadine.

*2 The numerous defendants-appellees sought to market generic versions of loratadine once the '233 patent expired. Seeking regulatory approval, each appellee submitted an application to the Food and Drug Administration (FDA). *See* 21 U.S.C. § 355(b), (j) (2000). Because Schering included the '716 patent in the Orange Book listing for loratadine, the applications also contained a certification that the '716 patent was invalid. *See id.* § 355(b)(2)(A), 355(j)(2)(A)(vii). The appellees notified Schering of the FDA filings. *See id.* § 355(b)(3)(B), 355(j)(2)(B)(ii).

After receiving notice of the FDA filings, Schering filed suit for infringement. *See* 35 U.S.C. § 271(e)(2)(A) (2000). After discovery, the parties filed cross motions for summary judgment on the validity issue. The district court construed claims 1 and 3 of the '716 patent to cover DCL in all its forms, including "metabolized within the human body" and "synthetically produced in a purified and isolated form." The parties agreed to that construction. Applying that claim construction, the district court found that the '233 patent did not expressly disclose DCL. Nonetheless, the district court also found that DCL was necessarily formed as a metabolite by carrying out the process disclosed in the '233 patent. The district court concluded that the '233 patent anticipated claims 1 and 3 of the '716 patent under 35 U.S.C. § 102(b). The district court therefore granted the appellees' motions for summary judgment of invalidity. Schering timely appealed to this court under 28 U.S.C. § 1295(a)(1) (2000).

II.

[1] This court reviews a grant of summary judgment without deference. *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1323 (Fed.Cir.2001). In reviewing a summary judgment determination, this court draws all reasonable inferences in favor of the non-movant. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986).

A.

2003 WL 21767852
--- F.3d ---
(Cite as: 2003 WL 21767852 (Fed.Cir.))

[2][3] A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. *Lewmar Marine, Inc. v. Barient, Inc.*, 827 F.2d 744, 747 (Fed.Cir.1987). Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. *Continental Can Co. v. Monsanto Co.* ., 948 F.2d 1264, 1268 (Fed.Cir.1991).

[4] At the outset, this court rejects the contention that inherent anticipation requires recognition in the prior art. Schering relies on *Elan Pharmaceuticals, Inc. v. Mayo Foundation for Medical Education & Research*, 304 F.3d 1221 (Fed.Cir.2002) for that proposition. This court has since vacated *Elan*. *See* 314 F.3d 1299 (Fed.Cir.2002). Other precedents of this court have held that inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. *E.g., In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1351 (Fed.Cir.2002); *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed.Cir.1999) ("Where ... the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results."); *Atlas Powder*, 190 F.3d at 1348-49 ("Because 'sufficient aeration' was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention.... An inherent structure, composition, or function is not necessarily known."). Thus, recognition by a person of ordinary skill in the art before the critical date of the '716 patent is not required to show anticipation by inherency. The district court therefore did not err in allowing for later recognition of the inherent characteristics of the prior art '233 patent.

*3 Contrary to Schering's contention, *Continental Can* does not stand for the proposition that an inherent feature of a prior art reference must be perceived as such by a person of ordinary skill in the art before the critical date. In *Continental Can*, this court vacated summary judgment of anticipation of claims reciting a plastic bottle with hollow ribs over a prior art reference disclosing a plastic bottle. The record contained conflicting expert testimony about whether the ribs of the prior art plastic bottle were solid. The accused infringer's expert testified that the prior art plastic bottle was made by blow molding, a process that would inherently produce hollow ribs. The patentee's experts testified that the prior art plastic bottle had solid ribs. The patentee disputed whether the blow molding inherently produced hollow ribs. Given the disputed material fact, this court vacated the summary judgment as improper. *Continental Can*, 948 F.2d at 1269. *Continental Can* makes no reference to whether the inherent feature, hollow ribs, was recognized before or after the critical date of the patent at issue. Read in context, *Continental Can* stands for the proposition that inherency, like anticipation itself, requires a determination of the meaning of the prior art. Thus, a court may consult artisans of ordinary skill to ascertain their understanding about subject matter disclosed by the prior art, including features inherent in the prior art. A court may resolve factual questions about the subject matter in the prior art by examining the reference through the eyes of a person of ordinary skill in the art, among other sources of evidence about the meaning of the prior art. Thus, in *Continental Can*, this court did not require past recognition of the inherent feature, but only allowed recourse to opinions of skilled artisans to determine the scope of the prior art reference.

Cases dealing with "accidental, unwitting, and unappreciated" anticipation also do not show that inherency requires recognition. *See Eibel Process Co. v. Minn. & Ontario Paper Co.*, 261 U.S. 45, 43 S.Ct. 322, 67 L.Ed. 523 (1923); *Tilghman v. Proctor*, 102 U.S. 707, 26 L.Ed. 279 (1880). In contrast to the present case, the record in *Eibel* and *Tilghman* did not show that the prior art produced the claimed subject matter. The patent at issue in *Tilghman* claimed a method of forming free fatty acids and glycerine by heating fats with water at high pressure. In *Tilghman*, the record did not show conclusively that the claimed process occurred in the prior art. In reviewing the prior art, the Court referred hypothetically to possible disclosure of the claimed process. For example, the Court stated "[w]e do not regard the accidental formation of fat acid in Perkins's steam cylinder ... (if the scum which rose on the water issuing from the ejection pipe was fat acid) as of any consequence in this inquiry." *Tilghman*, 102 U.S. at 711. In *Eibel*, the Court found no evidence of the claimed subject matter in the prior art. *Eibel*, 261 U.S. at 66 ("[W]e find no evidence that any pitch of the wire ... had

brought about such a result ... and ... if it had done so under unusual conditions, accidental results, not intended and not appreciated, do not constitute anticipation.").

*4 Applying an inherency principle in the context of an on sale bar under 35 U.S.C. § 102(b), this court has distinguished *Eibel* and *Tilghman*. *See Abbott Labs. v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1319 (Fed.Cir.1999) ("If a product that is offered for sale inherently possesses each of the limitations of the claims, then the invention is on sale, whether or not the parties to the transaction recognize that the product possesses the claimed characteristics."); *Scaltech, Inc. v. Retec/Tetra, LLC*, 269 F.3d 1321, 1330 (Fed.Cir.2001) ("[A]ppreciation of the invention is not a requirement to trigger the statutory [on sale] bar."). In those cases, the product sold or offered for sale had an inherent, but unrecognized, feature that was a limitation of the asserted claims. *Id.* Thus, this court has distinguished *Eibel* and *Tilghman*, which therefore do not bind this court to find no anticipation because skilled artisans did not recognize that the prior art '233 patent inherently produced the claimed invention, DCL.

In the context of accidental anticipation, DCL is not formed accidentally or under unusual conditions when loratadine is ingested. The record shows that DCL necessarily and inevitably forms from loratadine under normal conditions. DCL is a necessary consequence of administering loratadine to patients. The record also shows that DCL provides a useful result, because it serves as an active non-drowsy antihistamine. In sum, this court's precedent does not require a skilled artisan to recognize the inherent characteristic in the prior art that anticipates the claimed invention.

B.

[5] This court recognizes that this may be a case of first impression, because the prior art supplies no express description of any part of the claimed subject matter. The prior art '233 patent does not disclose any compound that is identifiable as DCL. In this court's prior inherency cases, a single prior art reference generally contained an incomplete description of the anticipatory subject matter, i.e., a partial description missing certain aspects. Inherency supplied the missing aspect of the description. Upon proof that the missing description is inherent in the prior art, that single prior art reference placed the claimed subject matter in the public domain. This case does not present the issue of a missing feature of the claimed invention. Rather, the new structure in this case, DCL, is not described by the prior ' 233 patent.

Patent law nonetheless establishes that a prior art reference which expressly or inherently contains each and every limitation of the claimed subject matter anticipates and invalidates. *See, e.g., EMI Group N. Am., Inc., v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1350 (Fed.Cir.2001) ("A prior art reference anticipates a patent claim if the reference discloses, either expressly or inherently, all of the limitations of the claim."); *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed.Cir.1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."). In these prior cases, however, inherency was only necessary to supply a single missing limitation that was not expressly disclosed in the prior art. This case, as explained before, asks this court to find anticipation when the entire structure of the claimed subject matter is inherent in the prior art.

*5 Because inherency places subject matter in the public domain as well as an express disclosure, the inherent disclosure of the entire claimed subject matter anticipates as well as inherent disclosure of a single feature of the claimed subject matter. The extent of the inherent disclosure does not limit its anticipatory effect. In general, a limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art. *See Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed.Cir.2001); *see also In re Kratz*, 592 F.2d 1169, 1174 (CCPA 1979) (suggesting inherent anticipation of a compound even though the compound's existence was not known).

In reaching this conclusion, this court is aware of *In re Seaborg*, 51 C.C.P.A. 1109, 328 F.2d 996 (CCPA 1964). In that case, this court's predecessor considered claims drawn to an isotope of americium made by nuclear reaction in light of a prior art patent disclosing a similar nuclear reaction process but with no disclosure of the claimed isotope. The

court reversed a United States Patent and Trademark Office rejection of the claims for lack of novelty. This court's predecessor found that the prior art process did not anticipate the claims because the process would have produced at most one billionth of a gram of the isotope in forty tons of radioactive material, i.e., the isotope would have been undetectable. *Id.* at 998-99 ("[T]he claimed product, if it was produced in the Fermi process, was produced in such minuscule amounts and under such conditions that its presence was undetectable."). In this case, DCL forms in readily detectable amounts as shown by the extensive record evidence of testing done on humans to verify the formation of DCL upon ingestion of loratadine.

[6] This court sees no reason to modify the general rule for inherent anticipation in a case where inherency supplies the entire anticipatory subject matter. The patent law principle "that which would literally infringe if later in time anticipates if earlier," *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1378 (Fed.Cir.2001), bolsters this conclusion. Similarly, "if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated." *Atlas Powder*, 190 F.3d at 1346. "The public remains free to make, use, or sell prior art compositions or processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate. The doctrine of anticipation by inherency, among other doctrines, enforces that basic principle." *Id.* at 1348. Thus, inherency operates to anticipate entire inventions as well as single limitations within an invention.

Turning to this case, the use of loratadine would infringe claims 1 and 3 of the '716 patent covering the metabolite DCL. This court has recognized that a person may infringe a claim to a metabolite if the person ingests a compound that metabolizes to form the metabolite. *See Hoechst-Roussel Pharms., Inc. v. Lehman*, 109 F.3d 756, 759 (Fed.Cir.1997) ("[T]he right to exclude may arise from the fact that when administered, [the accused product] metabolizes into another product ... which Hoechst has claimed."); *see also Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1421-22 (Fed.Cir.1994) (stating that a compound claim could cover a compound formed upon ingestion). An identical metabolite must then anticipate if earlier in time than the claimed compound.

*6 The record shows that the metabolite of the prior art loratadine is the same compound as the claimed invention. Claims 1 and 3 are compound claims in which individual compounds are claimed in the alternative in Markush format. DCL is within the scope of claims 1 and 3. Because the prior art metabolite inherently disclosed DCL, claims 1 and 3 are anticipated and invalid. In other words, the record shows that a patient ingesting loratadine would necessarily metabolize that compound to DCL. That later act would thus infringe claims 1 and 3. Thus, a prior art reference showing administration of loratadine to a patient anticipates claims 1 and 3.

C.

This court next examines whether Schering's secret tests of loratadine before the critical date placed DCL in the public domain. Before the critical date, Schering only tested loratadine in secret. Thus, according to Schering, "DCL was not publicly used, or described in any printed publication, until after February 15, 1983, the critical date for the '716 patent under 35 U.S.C. § 102(b)." Schering thus argues that DCL did not "exist" in the public domain such that DCL could be prior art against the '716 patent.

[7] Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. *In re Donohue*, 766 F.2d 531, 533 (Fed.Cir.1985). Thus, actual administration of loratadine to patients before the critical date of the '716 patent is irrelevant. The '233 patent suffices as an anticipatory prior art reference if it discloses in an enabling manner the administration of loratadine to patients.

[8] Thus, this court examines whether the '233 patent contains an enabling disclosure of DCL. A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter. *Bristol Myers*, 246 F.3d at 1379; *see also In re Donohue*, 766 F.2d at 533 (sustaining an anticipation rejection over a reference disclosing a compound and other references disclosing sufficient

information to make that compound). Indeed, information arising after the critical date may show that the claimed subject matter, as disclosed in a prior art reference, "was in the public's possession." *Bristol Myers*, 246 F.3d at 1379 (citing *In re Donohue*, 766 F.2d at 534).

An anticipatory reference need only enable subject matter that falls within the scope of the claims at issue, nothing more. To qualify as an enabled reference, the '233 patent need not describe how to make DCL in its isolated form. The '233 patent need only describe how to make DCL in any form encompassed by a compound claim covering DCL, e.g., DCL as a metabolite in a patient's body. The '233 patent discloses administering loratadine to a patient. A person of ordinary skill in the art could practice the '233 patent without undue experimentation. The inherent result of administering loratadine to a patient is the formation of DCL. The '233 patent thus provides an enabling disclosure for making DCL.

D.

*7 Finally, this court's conclusion on inherent anticipation in this case does not preclude patent protection for metabolites of known drugs. With proper claiming, patent protection is available for metabolites of known drugs. *Cf. In re Kratz*, 592 F.2d 1169, 1174 (CCPA 1979) (stating that a naturally occurring strawberry constituent compound does not anticipate claims to the substantially pure compound); *In re Bergstrom*, 57 C.C.P.A. 1240, 427 F.2d 1394, 1401-02 (CCPA 1970) (stating that a material occurring in nature in less pure form does not anticipate claims to the pure material).

[9] But those metabolites may not receive protection via compound claims. In this case, for instance, claims 1 and 3 broadly encompass compounds defined by structure only. Such bare compound claims include within their scope the recited compounds as chemical species in any surroundings, including within the human body as metabolites of a drug. As this case holds, these broad compound claims are inherently anticipated by a prior art disclosure of a drug that metabolizes into the claimed compound.

A skilled patent drafter, however, might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form, as in *Kratz* and *Bergstrom*, or as a pharmaceutical composition (e.g ., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition. The '233 patent would not provide an enabling disclosure to anticipate such claims because, for instance, the '233 patent does not disclose isolation of DCL.

The '716 patent contains claims 5-13 covering pharmaceutical compositions and claims 14-16 covering methods of treating allergic reactions by administering compounds that include DCL. These claims were not found anticipated by the '233 patent.

III.

The district court found that "there is no genuine issue that the consumption of loratadine by humans, with a wide variety of health statuses, necessarily results in the natural production in the human body of the DCL metabolite." This court must also examine the record for any genuine issue of material fact about whether ingestion of loratadine necessarily produces DCL. The record does, for instance, contain expert testimony, including a proposed metabolic scheme and animal data, that questions whether ingestion of loratadine always forms DCL.

A dispute about a material fact is genuine "if the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986). In this case, the evidence supporting the district court's conclusion is extensive. In thirteen clinical studies that Schering ran before May 1, 1987, all 144 patients involved had measurable amounts of DCL in their systems after ingesting loratadine. The district court found "no reports in any of the studies of any individual who did not metabolically produce DCL following the administration of loratadine." The appellees reported twenty-one clinical studies in which loratadine was administered to a total of 864 patients, all of whom formed measurable amounts of DCL in their systems. In addition, the record shows that since 1985 Schering's technical articles and Securities and Exchange Commission filings

referred to DCL as the metabolite of loratadine. Also the Food and Drug Administration, the corresponding European agency, the Physician's Desk Reference, and Schering's CLARITIN package insert referred to DCL as the major metabolite of loratadine.

*8 The record presents no data on humans to show that a genuine factual dispute exists about the formation of DCL after ingesting loratadine. Indeed Schering's own expert testified that no human has been found that does not metabolize loratadine to DCL, and that "[t]here is no scientific data in the published literature that says that DCL is not formed from loratadine in humans." Based on this record, no reasonable jury could find that DCL is not produced when a human ingests loratadine. This court therefore discerns no genuine issue of material fact.

CONCLUSION

The district court did not err in finding that the '233 patent discloses administering loratadine to a patient, and that DCL forms as a natural result of that administration. The district court correctly concluded that DCL is inherent in the prior art. Without any genuine issues of material fact, the district court correctly granted summary judgment that claims 1 and 3 are invalid as anticipated by the '233 patent.

COSTS

Each party shall bear its own costs.

AFFIRMED.

FN1. Prophetic examples are set forth in the present tense to indicate that they were not carried out. *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1578 (Fed.Cir.1984).

2003 WL 21767852, 2003 WL 21767852 (Fed.Cir.)

END OF DOCUMENT

PDR®

56

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2002

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ISBN: 1-56363-411-2

—Cont.

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bilis
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AND RAPID BLOOD AND URINE LEVELS
TIC ARE INDICATED, THERAPY WITH
RBENICILLIN DISODIUM) SHOULD BE
Y PARENTERAL ADMINISTRATION FOL-
HE PHYSICIAN'S DISCRETION, BY ORAL

tibility testing should be performed prior to
e course of therapy to detect the possible
esistant organisms which may develop.

ICATIONS

linarily contraindicated in patients who have
illin allergy.

casionally fatal hypersensitivity (anaphylac-
ave been reported in patients on oral penicil-
though anaphylaxis is more frequent follow-
l therapy, it has occurred in patients on oral
ese reactions are more apt to occur in indi-
history of penicillin hypersensitivity and/or a
sitivity to multiple allergens.
en reports of individuals with a history of pen-
nsitivity who have experienced severe hyper-
actions when treated with a cephalosporin,
a. Before initiating therapy with a penicillin,
y should be made concerning previous hyper-
ctions to penicillins, cephalosporins, or other
n allergic reaction occurs, the drug should be
and the appropriate therapy instituted.
APHYLACTOID REACTIONS REQUIRE IM-
MERGENCY TREATMENT WITH EPINEPH-
EN, INTRAVENOUS STEROIDS AND AIR-
AGEMENT, INCLUDING INTUBATION,
SO BE ADMINISTERED AS INDICATED.

ONS

with any penicillin preparation, an allergic re-
ding anaphylaxis, may occur particularly in a
e individual.
e of Geocillin may result in the overgrowth of
le organisms. If superinfection occurs during
opriate measures should be taken.
icillin is primarily excreted by the kidney, pa-
vere renal impairment (creatinine clearance of
ml/min) will not achieve therapeutic urine lev-
icillin.
with creatinine clearance of 10–20 ml/min it
sary to adjust dosage to prevent accumulation

Tests: As with other penicillins, periodic as-
rgan system function including renal, hepatic,
poietic systems is recommended during pro-
py.
tions: Geocillin (carbenicillin indanyl sodium)
may be increased and prolonged by concurrent
on of probenecid.
sis, Mutagenesis, Impairment of Fertility:
long-term animal or human studies to evalu-
nic potential. Rats fed 250–1000 mg/kg/day for
eveloped mild liver pathology (e.g., bile duct hy-
all dose levels, but there was no evidence of
l neoplasia. Geocillin administered at daily
g to 1000 mg/kg had no apparent effect on the
productive performance of rats.
Category B: Reproduction studies have been
t dose levels of 1000 or 500 mg/kg in rats, 200
e, and at 500 mg/kg in monkeys with no harm
to Geocillin. There are, however, no adequate
trolled studies in pregnant women. Because an-
action studies are not always predictive of hu-
se, this drug should be used during pregnancy
ly needed.
Delivery: It is not known whether the use of
humans during labor or delivery has immediate
dverse effects on the fetus, prolongs the dura-
or increases the likelihood that forceps delivery
etrical intervention or resuscitation of the new-
necessary.
thers: Carbenicillin class antibiotics are ex-
lk although the amounts excreted are unknown;
ution should be exercised if administered to a
nan.
e: Since only limited clinical data is available
ildren, the safety of Geocillin administration in
up has not yet been established.

REACTIONS

g adverse reactions have been reported as pos-
l to Geocillin administration in controlled stud-
clude 344 patients receiving Geocillin.
inal: The most frequent adverse reactions as-
h Geocillin therapy are related to the gastroin-
t. Nausea, bad taste, diarrhea, vomiting, flatu-

Dermatologic: Hypersensitivity reactions such as skin rash, urticaria, and le[illegible]quently pruritus.
Hematologic: As wit[illegible]r penicillins, anemia, thrombocytopenia, leukopenia, neutropenia, and eosinophilia have infrequently been observed. The clinical significance of these abnormalities is not known.
Miscellaneous: Other reactions rarely reported were hyperthermia, headache, itchy eyes, vaginitis, and loose stools.
Abnormalities of Hepatic Function Tests: Mild SGOT elevations have been observed following Geocillin administration.

OVERDOSAGE

Geocillin is generally nontoxic. Geocillin when taken in excessive amounts may produce mild gastrointestinal irritation. The drug is rapidly excreted in the urine and symptoms are transitory. The usual symptoms of anaphylaxis may occur in hypersensitive individuals.
Carbenicillin blood levels achievable with Geocillin are very low, and toxic reactions as a function of overdosage should not occur systematically. The oral LD_{50} in mice is 3,600 mg/kg, in rats 2,000 mg/kg, and in dogs is in excess of 500 mg/kg. The lethal human dose is not known.
Although never reported, the possibility of accumulation of indanyl should be considered when large amounts of Geocillin are ingested. Free indole, which is a phenol derivative, may be potentially toxic. In general 8–15 grams of phenol, and presumably a similar amount of indole, are required orally before toxicity (peripheral vascular collapse) may occur. The metabolic by-products of indole are nontoxic. In patients with hepatic failure it may be possible for unmetabolized indole to accumulate.
The metabolic by-products of Geocillin, indanyl sulfate and glucuronide, as well as free carbenicillin, are dialyzable.

DOSAGE AND ADMINISTRATION

Geocillin is available as a coated tablet to be administered orally.

Usual Adult Dose

URINARY TRACT INFECTIONS	
Escherichia coli, Proteus species, and *Enterobacter*	1–2 tablets 4 times daily
Pseudomonas and *Enterococcus*	2 tablets 4 times daily
PROSTATITIS	
Escherichia coli, Proteus mirabilis, Enterobacter and *Enterococcus*	2 tablets 4 times daily

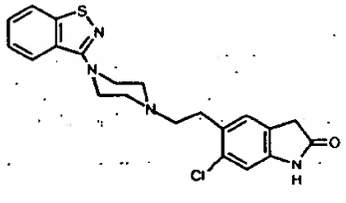
HOW SUPPLIED

Geocillin is available as film-coated tablets in bottles of 100's (NDC 0049-1430-66), and unit-dose packages of 100 (10 × 10's) (NDC 0049-1430-41). Each tablet contains carbenicillin indanyl sodium equivalent to 382 mg of carbenicillin.
Revised Sept. 1991 69-1970-00-2

GEODON™ Rx
(ziprasidone HCl)

DESCRIPTION

GEODON™ is available as GEODON Capsules (ziprasidone hydrochloride) for oral administration. Ziprasidone is an antipsychotic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl] ethyl] -6- chloro-1, 3-dihydro -2*H*- indol-2-one. The empirical formula of $C_{21}H_{21}ClN_4OS$ (free base of ziprasidone) represents the following structural formula:



GEODON Capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, monohydrochloride, monohydrate. The empirical formula is $C_{21}H_{21}ClN_4OS{\cdot}HCl{\cdot}H_2O$ and its molecular weight is 467.42. Ziprasidone hydrochloride monohydrate is a white to slightly pink powder.
GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. GEODON Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

CLINICAL PHARMACOLOGY

Pharmacodynamics

5HT_{1D}, and α_1-adrenergic receptors (K_i's of 4.8, 7.2, 0.[illegible] 3.4, 2, and 10 nM, respec[illegible]), and moderate affinity the histamine H_1 recepto[illegible]47 nM). Ziprasidone [illegible] tioned as an antagonist at the D_2, 5HT_{2A}, and 5HT_{1D} re[illegible] tors, and as an agonist at the 5HT_{1A} receptor. Ziprasi[illegible] inhibited synaptic reuptake of serotonin and norepine[illegible] rine. No appreciable affinity was exhibited for other re[illegible] tor/binding sites tested, including the cholinergic mu[illegible] rinic receptor (IC_{50} >1 μM).
The mechanism of action of ziprasidone, as with other dr[illegible] having efficacy in schizophrenia, is unknown. However[illegible] has been proposed that this drug's efficacy in schizophre[illegible] is mediated through a combination of dopamine type 2 [illegible] and serotonin type 2 (5HT_2) antagonism. Antagonism at [illegible] ceptors other than dopamine and 5HT_2 with similar re[illegible] tor affinities may explain some of the other therapeutic [illegible] side effects of ziprasidone.
Ziprasidone's antagonism of histamine H_1 receptors may [illegible] plain the somnolence observed with this drug.
Ziprasidone's antagonism of α_1-adrenergic receptors [illegible] explain the orthostatic hypotension observed with this [illegible]
Pharmacokinetics
Ziprasidone's activity is primarily due to the parent [illegible] The multiple-dose pharmacokinetics of ziprasidone [illegible] dose-proportional within the proposed clinical dose ra[illegible] and ziprasidone accumulation is predictable with mult[illegible] dosing. Elimination of ziprasidone is mainly via hepatic [illegible] tabolism with a mean terminal half-life of about 7 h[illegible] within the proposed clinical dose range. Steady-state [illegible] centrations are achieved within one to three days of do[illegible]
The mean apparent systemic clearance is 7.5 mL/min/[illegible] Ziprasidone is unlikely to interfere with the metabolism [illegible] drugs metabolized by cytochrome P450 enzymes.
Absorption: Ziprasidone is well absorbed after oral ad[illegible] istration, reaching peak plasma concentrations in 6[illegible] hours. The absolute bioavailability of a 20 mg dose [illegible] fed conditions is approximately 60%. The absorption [illegible] ziprasidone is increased up to two-fold in the pres[illegible] food.
Distribution: Ziprasidone has a mean apparent volu[illegible] distribution of 1.5 L/kg. It is greater than 99% boun[illegible] plasma proteins, binding primarily to albumin and [illegible] glycoprotein. The *in vitro* plasma protein bindin[illegible] ziprasidone was not altered by warfarin or propranolo[illegible] highly protein-bound drugs, nor did ziprasidone alt[illegible] binding of these drugs in human plasma. Thus, the p[illegible] tial for drug interactions with ziprasidone due to di[illegible] ment is minimal.
Metabolism and Elimination: Ziprasidone is extens[illegible] metabolized after oral administration with only a[illegible] amount excreted in the urine (<1%) or feces (<4%) [illegible] changed drug. Ziprasidone is primarily cleared via [illegible] metabolic routes to yield four major circulating metabo[illegible] benzisothiazole (BITP) sulphoxide, BITP-sulf[illegible] ziprasidone sulphoxide, and S-methyl-dihydrozipra[illegible] Approximately 20% of the dose is excreted in the urine [illegible] approximately 66% being eliminated in the feces [illegible] changed ziprasidone represents about 44% of total [illegible] related material in serum. *In vitro* studies using h[illegible] liver subcellular fractions indicate that S-methyl-[illegible] droziprasidone is generated in two steps. The data in[illegible] that the reduction reaction is mediated by aldehyde [illegible] and the subsequent methylation is mediated by thio[illegible] yltransferase. *In vitro* studies using human li[illegible] crosomes and recombinant enzymes indicate that CY[illegible] is the major CYP contributing to the oxidative meta[illegible] of ziprasidone. CYP1A2 may contribute to a much [illegible] tent. Based on *in vivo* abundance of excretory meta[illegible] less than one-third of ziprasidone metabolic clearance [illegible] diated by cytochrome P450 catalyzed oxidation and [illegible] imately two-thirds via reduction by aldehyde oxidase[illegible] are no known clinically relevant inhibitors or inducers [illegible] dehyde oxidase.
Special Populations
Age and Gender Effects—In a multiple-dose [illegible] treatment) study involving 32 subjects, there was [illegible] ence in the pharmacokinetics of ziprasidone bet[illegible] and women or between elderly (>65 years) and yo[illegible] 45 years) subjects. Additionally, population pha[illegible] netic evaluation of patients in controlled trials h[illegible] no evidence of clinically significant age or ge[illegible] differences in the pharmacokinetics of ziprasido[illegible] modifications for age or gender are, therefore, [illegible] mended.
Race—No specific pharmacokinetic study was [illegible] investigate the effects of race. Population pha[illegible] evaluation has revealed no evidence of clinically [illegible] race-related differences in the pharmac[illegible] ziprasidone. Dosage modifications for race [illegible] not recommended.
Smoking—Based on *in vitro* studies utilizing [illegible] enzymes, ziprasidone is not a substrate for C[illegible] ing should therefore not have an effect on the [illegible] netics of ziprasidone. Consistent with these [illegible] population pharmacokinetic evaluation has [illegible] any significant pharmacokinetic differences [illegible] ers and nonsmokers.
Renal Impairment—Because ziprasidone is [illegible] lized, with less than 1% of the drug excreted [illegible] nal impairment alone is unlikely to have a [illegible] the pharmacokinetics of ziprasidone. The [illegible] of ziprasidone following 8 days of 20 mg [illegible]

[illegible]icating th[illegible] al impair[illegible] yed by her[illegible] patic Impe[illegible] lly by the li[illegible] expected t[illegible] dose study at [illegible] inically sign[illegible] revealed an in[illegible] ugh Class A [illegible] ntrol group [illegible] ubjects with [illegible] Group.
Drug-Drug Int[illegible]
In vitro en[illegible] icrosomes sh[illegible] ect on CYP1A[illegible] and thus woul[illegible] drugs primaril[illegible] ve have reveal[illegible] inetics of dex[illegible] ithium (see Dr[illegible]
In vivo studies[illegible] ase in ziprasi[illegible] arbamazepine [illegible] ziprasidone AU[illegible] ine, but no effe[illegible] xidine or anti[illegible]
TIONS).
Clinical Trials
The efficacy of zi[illegible] nd evaluated i[illegible] and 6-week) t[illegible] ials were in in[illegible] ia for schizop[illegible] ses of ziprasid[illegible] able to di[illegible] m-term study [illegible] ebo arm wa[illegible] of the three [illegible] ziprasidone and h[illegible] ical instrume[illegible] ms and sympto[illegible] ing Scale (BP[illegible] ood Scale (PA[illegible] ral psychopa[illegible] of drug treat[illegible] cluster (conce[illegible] suspiciousn[illegible] ed a particul[illegible] osic schizoph[illegible] ent, the Clini[illegible] ation of a sl[illegible] ifestations of [illegible] of the patie[illegible] ore Sympton[illegible] re symptoms [illegible] ints of the t[illegible] 4-week, pla[illegible] doses of zip[illegible] ly the 60 m[illegible] BS total sc[illegible] dose group w[illegible] ms cluster or [illegible] 6-week, pla[illegible] doses of zipr[illegible] both dose gro[illegible] otal score, th[illegible] core and th[illegible] Although 80 [illegible] and 40 mg BID[illegible]
[illegible] week, plac[illegible] doses of zipra[illegible] all three do[illegible] BS total scor[illegible] uster, and th[illegible] group was [illegible] cale score.[illegible] relationship[illegible]
[illegible] week, place[illegible] of zipras[illegible] roups was s[illegible] interest.[illegible] ects condu[illegible] henic inpa[illegible] sidone ([illegible] 52 weeks.[illegible] relapse", [illegible] or very [illegible] e) on the [illegible] 0 in two cr[illegible] perior to [illegible] with n[illegible] groups.[illegible] sufficient [illegible] and race.[illegible] der did no[illegible]
[illegible] AND T[illegible]